REMARKS

Claims 33-38 are pending in the instant application. Claims 39-43 have been cancelled without prejudice or disclaimer. Applicants reserve the right to pursue the cancelled subject matter in related applications.

Claims 33, and 36 are presently amended so as to recite "relative to a sample from an individual not suffering from Sjögren's disease." Support for these amendments may be found in the specification as filed, for example, at page 128, line 28, through page 129, line 12. Accordingly, no new matter has been introduced.

I. Rejections Under 35 U.S.C. §§ 101 and 112

A. The Examiner rejects claims 33-43, under 35 U.S.C. § 101 as allegedly not being "supported by either a specific and substantial asserted utility or a well established utility, for reasons of record in the previous Office Action, Paper No. 13, at pages 3-5." *See*, Paper No. 15, page 2. The Examiner finds Applicants' assertions of utility to be unconvincing. In rejecting the instant claims, the Examiner states:

> [b]ecause the specification has not provided any evidence that neutrokine-α or APRIL are differentially expressed in Sjogren's disease (or any asserted disease listed), and presents an extensive list of diseases or disorders that may be diagnosed using the TR18 polypeptides, the method of detecting Sjogren's disease is not a specific and substantial utility. At the time of filing of the instant application, there was no nexus between differential expression of neutrokine-α or APRIL and Sjogren's disease. . . . . Utility has to be established as of when the invention was made, and all Applicants had was an invitation to experiment.

See, Paper No. 15, page 4. Applicants respectfully disagree and traverse the rejection.

(i) The asserted utility of the instant invention is both specific and substantial

Applicants contend that the assertion of utility made for TR18 of the present

invention, that it is useful in the diagnosis of Sjögren's disease, is both specific and substantial. Applicants disclose in the specification the TR18 polypeptide that binds to the ligand neutrokine-alpha. Based upon this biological function is made the assertion that compounds of the present invention may be useful to diagnose autoimmune disorders including Sjögren's disease. Moreover, Applicants have provided evidence that expression of identified TR18 ligands is altered in Sjögren's disease. As such, Applicants submit that adequate proof of a biological activity of TR18 has been shown, thereby constituting a showing of practical utility.

Applicants respectfully submit that TR18 of the invention (such as, for example, the polypeptide shown as SEQ ID NO:2), has an immediate and specific utility. Such polypeptide may be used to detect Sjögren's disease. The specification as filed discloses TR18, a novel TNF receptor family member that is expressed on B cells and binds neutrokine-alpha. At the time of filing of the present application neutrokine-alpha was known to enhance B-cell proliferation, differentiation, and/or survival, and to enhance immunoglobulin production. Patients suffering from autoimmune diseases such as Sjögren's disease were known to exhibit increased levels of autoreactive antibodies, and therefore, factors which regulate antibody production would have been useful as markers for such disorders. Given the nexus between the function of TR18, the enhancement of antibody production induced by the TR18 ligand (neutrokine-alpha), and the increased autoantibody production seen in autoimmune diseases including Sjögren's disease, one of skill in the art would have been able to routinely use the compositions of the present invention in the detection of Sjögren's disease. Accordingly, polypeptides of the invention are supported by an immediate utility that is both specific and substantial.

a) Specific

The test for specificity of such an assertion is whether said utility is specific to the subject matter claimed, in contrast to a utility that would be applicable to the broad class of the invention, such as use of a complex machine for landfill. *See*, Utility Examination Guidelines. The disclosed utilities for TR18 discussed above are specific, in that not every protein (nor every TNF receptor family member) may be used to diagnose autoimmune diseases including humoral mediated autoimmune diseases such as Sjögren's disease. Consequently, the skilled artisan would most certainly not consider such a use to be a "throw-away utility" such as landfill. Furthermore, where an applicant discloses a biological activity (*e.g.*, the specific binding of a known ligand), and reasonably correlates that activity to a disease or condition (*e.g.*, Sjögren's disease), the applicant has sufficiently identified a specific utility for the invention. M.P.E.P. § 2107.01 at 2100-32 (emphasis added). Applicants submit that, based on the instant disclosure, the skilled artisan would be convinced that the asserted use in the diagnosis of autoimmune disorders including humoral mediated autoimmune diseases such as Sjögren's disease does constitute a specific utility.

b) Substantial

Moreover, the use of TR18 polypeptides to diagnose autoimmune diseases including humoral mediated autoimmune diseases such as Sjögren's disease are substantial, as "the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." *See*, Revised Interim Utility Guidelines Training Materials, page 6. Pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy 35 U.S.C. § 101. *See, Nelson v. Bowler*, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980); *See also,* M.P.E.P. §2107.01(III). It is well-established that the mere identification of a pharmacological activity of a compound that is

relevant to an asserted pharmacological use provides an "immediate benefit to the public" and satisfies the utility requirement. *Id.* Accordingly, the utilities asserted by Applicants are clearly substantial.

In light of the above comments, Applicants contend that the asserted use of the present invention in the detection of Sjögren's disease is both specific (not every protein may be used to detect Sjögren's disease) and substantial ("treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." (Revised Interim Utility Guidelines Training Materials, p. 6)) as required under 35 U.S.C. § 101. Furthermore, although the Examiner did not explicitly raise the issue of credibility, Applicants assert that the asserted utility is also credible.

(ii) The asserted utility of the instant invention was credible at the time of filing

Applicants contend that the assertion of utility made for TR18 of the present invention, that it is useful in the diagnosis of humoral mediated autoimmune diseases such as Sjögren's disease, would have been credible to one of ordinary skill in the art as of the date the instant application was filed.

Applicants respectfully point out that at the priority date of the instant application, Sjögren's disease was known to be a humoral mediated autoimmune disease[1], and that elevated levels of autoantibodies are found in the serum of Sjögren's disease patients. Applicants particularly point to the contents of Table 21-1 on page 320 of Exhibit A, where Sjögren's disease is identified as an autoimmune disease on the basis of "multiple tissue antibodies, a specific non-histone ANA[2] (SS-B)." Furthermore, on the priority date of the instant application, one of skill in the art would have appreciated that the presence

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[1] *See*, e.g., Exhibit A, Berkow, R. et al. (Eds.). 'The Merck Manual of Diagnosis and Therapy (Fifteenth Edition)', Merck & Co., Inc., N.J., at pages 319 to 322 (1987)

[2] ANA – Antinuclear antibody.

of autoantibodies was a characteristic of Sjögren's disease[3]. Indeed, Exhibit B teaches that

> remarkable immunologic activity, detected in blood serum, is characteristic of SS; most patients have elevated levels of antibodies against γ-globulin, nuclear protein, and many tissue constituents. Precipitating antibodies to nuclear antigens (identified by immunodiffusion analysis), termed SS-B antibodies, are highly specific for primary SS.

See, Exhibit B at page 1250, lines 28-32.

Applicants respectfully point out that all antibodies are produced by B-lymphocytes, and that the instant application discloses that TR18 of the present invention is preferentially expressed by mature B-lymphocytes. *See e.g.*, specification at page 122, line 17. Furthermore, the application teaches that TR18 of the present invention binds neutrokine-alpha, a Tumor Necrosis Factor family ligand known to play a role in the regulation of B-cell proliferation, differentiation, and/or survival, as well as to enhance immunoglobulin production. *See e.g.*, specification at page 11, lines 25-28; and at page 12, lines 23-28. The specification further discloses that a person suffering from an autoimmune disorder may exhibit elevated levels of expression of neutrokine-alpha, and therefore, that polynucleotides, polypeptides, and antibodies of the invention may be useful in diagnostic applications, which include the diagnosis of autoimmune disorders including, specifically Sjögren's disease. *See e.g.*, specification at page 122, line 16 through page 123, line 5; and at page 128, lines 15 and 20-27.

Therefore, given (a) the expression profile of TR18, (b) the ability of TR18 to bind ligands known to regulate B-cell proliferation, differentiation, and/or survival, as well as to enhance immunoglobulin production, (c) the widely accepted role of B-cells in producing immunoglobulin (antibody) molecules, and (d) the characteristic autoantibody production found in serum of Sjögren's disease patients, one of skill in the art would have appreciated that a nexus exists between the polypeptides of the invention and their use in

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[3] *See*, e.g., Exhibit B, Berkow, R. et al. (Eds.). 'The Merck Manual of Diagnosis and Therapy (Fifteenth Edition)', Merck & Co., Inc., N.J., at pages 1249 to 1250 (1987)

diagnosing humoral mediated autoimmune diseases such as Sjögren's disease. Accordingly, Applicants submit that the asserted utility of TR18 in the diagnosis of Sjögren's disease would have been credible to one of skill in the art, and that one of skill in the art would have been able to routinely use the claimed methods.

(iii) The asserted utility of the instant invention is independently corroborated

Furthermore, Applicants respectfully point out, that expression levels of neutrokine-alpha have been shown to be elevated in Sjögren's disease. As Applicants have previously demonstrated, it is clear that those of skill in the relevant art believe that Neutrokine-alpha levels are diagnostic of Sjögren's disease. Indeed, the Examiner has noted that post-filing publications do indeed support Applicants' assertion of utility:

> [t]he publications of Groom et al. and Mariette et al. support the assertion that the TR18 receptor of the instant invention could be used diagnostically to detect Sjogren's disease.

See, Paper No. 15, at page 3, lines 20-22.

Legal precedent for the use of post-filing date references in this manner can be found in *In re Brana*, where the courts stated:

> The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi,* 439 F.2d at 224 n.4, 169 U.S.P.Q. (BNA) at 370 n.4.

See, *In re Brana*, 51 F.3d 1560 at 1567 n.19, 34 U.S.P.Q.2D (BNA) 1436 (March 30, 1995). Applicants point out that as conceded by the Examiner, Groom et al. (*J. Clin. Invest.* (2002) 109:59-68) and Mariette et al. (*Ann. Rheum. Dis.* (2003) 62:168-171) demonstrate that Neutrokine-alpha levels are elevated in patients with Sjögren's disease and it is clear from statements made in these publications that the authors believe that Neutrokine-alpha levels are a good indicator, *i.e.*, diagnostic marker, of Sjögren's disease.

Applicants note that the supportive evidence cited in Groom *et al.* and Mariette *et al.*, dated after the applicants' filing date, "can be used to substantiate any doubts as to asserted utility since it pertains to the accuracy of a statement already in the specification." *See e.g.*, *In re Brana*, 51 F.3d 1560 at 1567 n.19, 34 U.S.P.Q.2D (BNA) 1436 (March 30, 1995). Thus, in accord with Brana, Groom et al. and Mariette et al. substantiate the use of TR18 polypeptides of the invention in diagnosing Sjögren's disease. Moreover, Applicants submit that the absence of evidence in the instant specification that "neutrokine-α or APRIL are differentially expressed in Sjögren's disease (or any asserted disease listed)" is an improper consideration for whether this utility, which is asserted in the specification, is specific and substantial. Accordingly, Applicants contend that the instant application asserts a credible utility for the present invention, *i.e.*, the detection of Sjögren's disease, and fulfills the requirements of 35 U.S.C. § 101.

(iv) The claimed invention meets the requirements of 35 U.S.C. § 101

In summary, the asserted utility for TR18 is specific (not every protein may be used to detect Sjögren's disease) and substantial ("the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." (Revised Interim Utility Guidelines Training Materials, p. 6)). In addition, these utilities are credible. The Examiner has failed, however, to provide any countervailing statements as to why these particular utilities are not specific, substantial and credible.

Even assuming, *arguendo,* the Examiner has established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that they have rebutted the Examiner's showing by proffering sufficient evidence to lead one skilled in the art to conclude that the asserted utilities are more likely than not true.

In view of the above, Applicants submit that the asserted utilities of the invention meet the statutory requirement set forth in 35 U.S.C. § 101. The Examiner has failed to establish and maintain grounds as to why a rejection for lack of utility is proper. Accordingly, Applicants respectfully request that the rejection of claims 33-43 under 35 U.S.C. § 101 be withdrawn.

B. The Examiner has also rejected claims 33-43 under 35 U.S.C. § 112, first paragraph, as allegedly not being "supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention".

In rejecting claims 41-43, the Examiner specifically states that:

> [t]he specification defines an antigenic epitope on page 55 as containing a sequence of at least 4 amino acids ... the basis of the method is the binding of the receptor of SEQ ID NO:2 to neutrokine-α in the biological sample ... [o]ne of ordinary skill in the art would not expect that a peptide fragment of 4 amino acids (or the other peptides of claim 42) would bind neutrokine-α with any type of specificity.

See, Paper No. 15, Page 5. Applicants respectfully traverse the rejection.

Applicants respectfully point out that rejected claims 39-43 have been cancelled without prejudice or disclaimer, thereby obviating their rejection. However, as detailed above, Applicants contend that the asserted utilities of the invention meet the statutory requirement set forth in 35 U.S.C. § 101 and, armed with the specification of the instant invention, one skilled in the art clearly would know how to use the claimed invention. Accordingly, the present rejection of claims 33-38 is improper and should be withdrawn.

Accordingly, Applicants respectfully request that the rejection of claims 33-43 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

C. The Examiner has also rejected claims 33-43 under 35 U.S.C. § 112, second paragraph, as allegedly failing "to particularly point out and distinctly claim the subject matter which applicants regard as the invention." *See*, Paper No. 15, Page 6. Applicants respectfully traverse this rejection.

Preliminarily, Applicants respectfully point out that rejected claims 39-43 have been cancelled without prejudice or disclaimer, thereby obviating their rejection.

The Examiner alleges "there are no control steps, such as comparing the degree of binding with a biological sample from a normal individual." See, Paper No. 15, page 6. Applicants have amended claims 33 and 36 to recite "relative to a sample from an individual not suffering from Sjögren's disease", thereby obviating the Examiner's objection on these grounds.

The Examiner further alleges that claims 33 and 36 are "incomplete method claims, and are not written with the different methods steps clearly recited." *See*, Paper No. 15, page 6. Applicants respectfully disagree and point out that the method steps of the presently rejected claims are proper and include contacting a biological sample with polypeptides of the invention, and assaying for binding of elements of the biological sample to the polypeptide of the invention. Accordingly, Applicants respectfully request that this basis of the rejection be reconsidered and withdrawn.

Accordingly, Applicants respectfully request that the rejection of claims 33-43 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the present application. The present application is believed to be in condition for allowance. Early notice to that effect is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below. If a fee is required in connection with this paper, please charge Deposit Account No. 08-3425 for the appropriate amount.

Respectfully submitted,

Dated: October 20, 2003

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Enclosures
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